istered to determine the influence of ISO on endothelial dependent and independent vasodilatation. In the control state (*p < 0.05), both IC-ACh and IC-SNP resulted in marked coronary vasodilatation (Δ CBF ACh 76 ± 6* ml/min and SNP 37 ± 7*) while IC-ANP did not alter CBF. IC-ISO increased basal CBF (52 ± 11 ml/min to 87 ± 21*) and LV contractility (+dP/dt 1803 ± 93 mmHgL/sec to 2395 ± 151*), and decreased coronary vascular resistance (CVR 2.6 ± 0.3 RU to 1.4 ± 0.2*) and coronary perfusion pressure (105 ± 7 mmHg to 87 ± 7*). In the presence of ISO, IC-ANP significantly increased CBF (87 ± 21 ml/min to 117 ± 26*) while ACh and SNP-mediated coronary vasodilation were similar to control changes.

In summary, IC-ISO augments ANP-mediated coronary vasodilatation but does not enhance ACh or SNP mediated vasodilatation. This observation suggests a functional link between the natriuretic peptide system and the β-adrenergic system in the control of CBF. The elevation in circulating catecholamines observed in CHF may, therefore, serve in part to augment endogenous ANP-mediated coronary vasodilation and thus be coronary protective in the progression of CHF.

MONDAY PM

930-107 Does the Abnormal Endothelial Response of the Human Coronary Vasculature in Atherosclerosis Extend Beyond the Muscarinic Receptor?

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To investigate whether atherosclerosis and its risk factors (RF) that are known to result in abnormal coronary vasodilator responses to muscarinic receptor stimulation with acetylcholine (ACH), are also associated with generalized endothelial receptor dysfunction, we compared the effects of substance P (SP) with those of ACH in the human coronary vasculature. In 25 patients, 7 (Group 1) with normal coronary arteries and no RF, and 18 (Group 2) with either RF for, or established atherosclerosis (>20% stenosis), intracoronary ACH (3, 30, 100, 300 μg/min) and SP (5, 10, 20 pmol/min) were given. Coronary blood flow was measured using a Doppler flow wire and epicardial coronary artery (ECA) diameter by quantitative angiography. *Results;* Microvascular dilation measured as a decrease in coronary vascular resistance (CVR) with ACH was greater compared to SP (−49 ± 23% vs. −24 ± 19% respectively, p < 0.01), but ECA dilation with SP was greater compared to ACH (0 ± 14% (ACH) vs. 16 ± 17% SP, p < 0.01).

	% change with ACH		% change with SP	
	CVR	ECA Diam	CVR	ECA Diam
Group 1	−65**	9**	−26**	22**
Group 2	−41**@	3@	−22**	13**@

*P < 0.05, **P < 0.01 cf. to baseline, @P < 0.05 Group 1 vs. Group 2

Group 2 pts had depressed microvascular and ECA dilation with ACH compared to Group 1 pts (Table). In contrast, with SP, microvascular dilation was similar in both groups, and ECA dilation was higher in those without RF; however, the correlation between the magnitude of ECA dilation with ACH and SP was weak (r = 0.21). Thus, there is a preponderance of muscarinic receptors in the microvessels, whereas SP receptors are located predominantly in human ECA. In pts with RF and atherosclerosis, ACH-induced endothelium-dependent ECA and microvascular dilation is depressed, but microvascular dilation with SP appears unaffected and SP-induced ECA dilation is only mildly reduced. Therefore, atherosclerosis and its RF appear to produce non-uniform dysfunction of various endothelial cell surface receptors in the human coronary vasculature.

931 Anti-Ischemic Agents and Mechanisms

Monday, March 20, 1995, 3:00 p.m.–5:00 p.m.
Ernest N. Morial Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

931-108 Parasympathetic Intervention Affects Ischemia by Increasing Coronary Flow in Normal, but not in Impaired Left Ventricular Function. A New Approach to Antiischemic Therapy?

Ad F.M. van den Heuvel, Martin van der Ent, Willem J. Remme. *Sticares Foundation, Rotterdam, The Netherlands*

Cardiovascular parasympathetic control reportedly is reduced in left ventricular (LV) dysfunction and in heart-failure. To evaluate whether parasympathetic intervention differentially affects coronary flow and ischemia in normal (N) vs impaired (I = ejection fraction <40%) LV-function, 17 pts in N and 7 pts in I received atropine before ischemia was induced by incremental atrial pacing. Placebo was administered to a matching control group (CN and CI, resp.). All pts had >70% left CAD. During maximal pacing, heart rate and rate pressure product (myocardial oxygen demand) where 7% and 12% higher in N, compared to CN, but were comparable in I and CI. Moreover, 1 minute post pacing these values were 8% and 12% higher, resp., N vs CN. Vasoconstrictive circulating neurohormones (norepinephrine) increased similarly in all groups. Coronary flow increased 23% more in N than in CN and to a similar extent in I and CI. Myocardial ischemia, as indicated by changes in myocardial lactate metabolism, was less in N [lactate extraction +10% (N) vs −21% (CN), −18% (I) and −19% (CI)]. Fifteen minutes after pacing, coronary flow was still decreased by 11% and coronary vascular resistance increased by 15% in CN, as compared to N. Thus, reduction of parasympathetic tone improves coronary flow and reduces myocardial ischemia in the latter, despite similar sympathetic activation and more pronounced myocardial oxygen demand in N. This supports a greater role for cardiovascular parasympathetic control of (diseased) coronary arterial system in normal LV-function and, possibly, a new area of intervention in antiischemic therapy in the latter.

931-109 Correlation Between Magnesium Deficiency and Disease Activity in Patients with Variant Angina and the Effect of Oral Magnesium Supplementation

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Purpose; We examined whether or not the degree of intracellular magnesium (Mg) deficiency correlates with disease activity of variant angina (VA) and the effect of oral Mg supplementation. *Methods;* Eighteen patients with VA (17 men and a woman) were divided into 2 groups according to the frequency of occurrence of angina attacks (inactive and active group > 3 angina attacks per week).

We measured Mg status by serum, urinary excretion, 24-hour Mg retention rate. Intracellular Mg content of mononuclear cell (MNC) and erythrocyte were also measured by atomic absorption spectrophotometry. We also examined the effect of oral Mg supplementation (Mg oxide 0.6 g/day, more than 2 months) to refractory patients (n = 4) with Mg deficiency. *Result;* There were no significant differences in serum Mg content between active and inactive groups. Urinary Mg excretion in a day in active group (136.4 ± 36.6 mg/dat) was significantly higher than in inactive group (59.1 ± 7.0; p < 0.05). Retention rate and intracellular Mg content of MNC and erythrocyte were 57.0 ± 7.3 vs 24.7 ± 3.2% (p < 0.01), 151.3 ± 14.4 vs 214.3 ± 8.0 fg/cell (p < 0.01) and 3.8 ± 0.5 vs 5.1 ± 0.4 fg/cell (p < 0.05), respectively. Retention rate and intracellular Mg content of MNC and erythrocyte correlated well with the frequency of angina attacks in these patients (r = 0.78, p < 0.01: r = 0.76, p < 0.01: r = −0.50, p < 0.05). With oral Mg supplementation, the response to calcium antagonist was improved, coupled with the increase of intracellular Mg content, from 151 ± 19.8 to 226.8 ± 17.0 fg/cell in MNC and from 3.0 ± 0.6 to 5.0 ± 0.3 fg/cell in erythrocyte.

Conclusion; It is concluded that the degree of intracellular Mg deficiency correlates well with disease activity of VA, suggesting that Mg deficiency plays an important role in accelerating disease activity. Oral Mg supplementation appears to be an effective and less expensive regimen for patients with VA.

931-110 Effects of NPC 15669 on Myocardial Stunning and Infarction Size

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Leukocytes have been implicated in myocardial infarction (MI) development and progression. We tested the efficacy of the novel leukocyte recruitment inhibitor NPC 15669 (Scios Nova, Inc.) on myocardial stunning (MS) and preconditioned MI. NPC is a member of the leumedins, and is an inhibitor of leukocyte adhesion to endothelium via blockage of integrin binding. We also show, that NPC 15669 have strong antiplatelet effects. In an open chested swine model, NPC 15669 (10 mg NPC/kg loading dose followed by constant infusion at 6 $mg/kg^{-1}/h^{-1}$) was administered in 6 animals. Myocardial thickening (MT) was determined by epicardial ultrasound. The left anterior descending artery was occluded for 8 min. followed by 90 min. of reperfusion, during which myocardial MT was recorded at regular intervals. We have found that treatment with NPC 15669 increases myocardial contractility and significantly decreases MS time compared to six controls (26.7 ± 4.0 min vs. 50.0 ± 4.3 min, p = 0.0026). This report also demonstrates the beneficial effects of NPC 15669 on myocardial tissue survival after a period of ischemia. In NPC 15669 treated animals 23.4 ± 6.7% of at risk tissue became necrotic compared to 53.0 ± 6.6% in controls, p = 0.0102. Our data suggests that NPC 15669 significantly reduces myocardial injury in both the stunning and infarction mod-

els. The precise mechanism of these effects is unknown, but may be related to the inhibition of platelet function and/or leukocyte recruitment.

931-111 Platelet Activation and Aggregation by Therapeutic Doses of Heparin

Zihui Xiao, Pierre Théroux, John R. Plachetka. *Montreal Heart Institute, Montreal, Quebec, Canada*

To understand better the complex interaction of heparin with platelets, this study investigated platelet function by flow cytometry and aggregation curves, with and without the drug, in 7 pts with unstable angina and 7 normal individuals. *Method and Results:* Platelet aggregation induced by low doses ADP (0.3125 μM) and thrombin receptor agonist peptide (TRAP 0.625 μM) was quantified in platelet-rich plasma (PRP) before and after the administration of intravenous heparin at doses prolonging the aPTT 2.5 × control and also after the addition in whole blood, *ex vivo* of therapeutic concentration of heparin (0.2 U/ml), argatroban (1 ng/ml) or of an equal volume of normal saline (Control). Platelet activation was evaluated by the percentage of fluorescein positive platelets (PL%) and the binding index per platelet (BI), using antibodies directed against P-selectin (CD62) and activated GP IIb/IIIa receptor (PAC-1). Following intravenous heparin, the maximal shift in platelet aggregation (Max%) increased from 6.3 ± 3.6 to 11.6 ± 8.5 with ADP and from 4.4 ± 3.0 to 11.9 ± 5.2 ($p < 0.05$) with TRAP. The results of the *ex vivo* studies (x ± SD) were:

	PAC-1		CD62		
	PL%	BI	PL%	BI	Max%
Control					
Basal	1.80 ± 0.67		0.66 ± 0.114	0.011 ± 0.0024	
ADP	70.1 ± 15.99	3.5 ± 1.48	10.1 ± 4.13	0.18 ± 0.074	4.3 ± 2.25
TRP	18.8 ± 16.45	0.81 ± 0.61	2.77 ± 2.02	0.05 ± 0.039	2.2 ± 1.84
Heparin					
Basal	3.60 ± 1.42*		1.00 ± 0.292*	0.018 ± 0.0047†	
ADP	76.6 ± 12.49*	4.2 ± 1.70*	13.2 ± 4.43*	0.24 ± 0.087*	8.8 ± 3.06†
TRP	32.9 ± 25.60*	1.5 ± 1.17*	3.32 ± 2.24*	0.06 ± 0.039	6.2 ± 1.84*
Argatroban					
Basal	2.30 ± 0.75		0.82 ± 0.192*	0.015 ± 0.0041*	
ADP	69.1 ± 19.62	3.5 ± 1.75	11.4 ± 4.42	0.21 ± 0.085	2.3 ± 2.07*
TRP	21.0 ± 14.23	0.88 ± 0.56	2.48 ± 1.12	0.05 ± 0.021	2.0 ± 2.61

*$p < 0.05$ and †$p < 0.01$ vs Control

Thus, heparin, but not argatroban, a direct thrombin inhibitor, induced P-selectin expression and GP IIb/IIIa activation in the basal state and following agonist stimulation at low concentrations.

931-112 A Low-dose Intravenous Aspirin, Bolus Injection, Effectively Inhibits Platelet Aggregation

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Prompt inhibition of platelet aggregation is important in acute coronary syndrome and before an intervention procedure. To determine whether a single low dose of iv aspirin inhibits platelet aggregation, twenty-seven healthy volunteers (7 F and 20 M), mean age 43.5 years, were randomized double-blind to a single iv low dose of aspirin DL-lysine (L-ASA) equivalent to 2 mg/kg of aspirin, high dose (H-ASA) equivalent to 10 mg/kg, or placebo (Pl). Platelet aggregation were performed before and 1 h and 24 h after drug administration, in whole blood (WB) using electrical impedance and in platelet-rich plasma (PRP) by optical light transmittance. Baseline WB platelet aggregation (Col 3 μg/ml) was the same with L-ASA, H-ASA and Pl (24 ± 5, 23 ± 3 and 24 ± 4Ω respectively) and decreased significantly more with L-ASA and H-ASA than with Pl after 1 h. (17 ± 6, 15 ± 7 and 21 ± 5Ω $p < 0.01$) and 24 h (17 ± 7, 16 ± 6 and 25 ± 4Ω $p < 0.01$). Results in PRP were similar:

PRP optical aggregation (%)		Before	After ASA	
			1 h.	24 h.
ADP (5 μM):	L-ASA	73 ± 21	50 ± 14*	45 ± 15*
	H-ASA	65 ± 23	54 ± 17*	52 ± 16*
	Pl	69 ± 18	72 ± 22	69 ± 14
Col (3 μg/ml):	L-ASA	64 ± 19	33 ± 13*	36 ± 18*
	H-ASA	60 ± 16	32 ± 17*	34 ± 14*
	Pl	55 ± 13	56 ± 18	57 ± 14

*$p < 0.001$ (ANOVA test) respect to Pl and the baseline values

No differences in response were observed between the two doses of aspirin and no significant changes occurred between 1 and 24 hours in any group.

Effective inhibition of platelet aggregation is thus achieved within 1 hour after the administration of low-dose 2 mg/kg of iv aspirin.

931-113 Demonstration of Potent Inhibition of Platelet Aggregation with an Orally Active GPIIb/IIIA Receptor Antagonist

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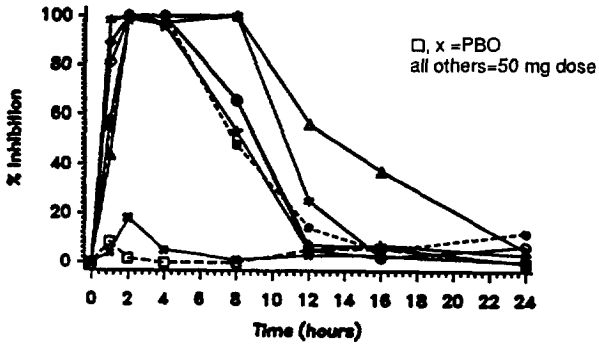
This single-blind, placebo-controlled study evaluated the tolerability and pharmacodynamic (PD) response of the first dose of the oral GPIIb/IIIa receptor antagonist, SC-54684A (ethyl 3S-[[4-[[4(amino-iminomethyl)phenyl]amino}-1,4-dioxobutyl]amino]-4-pentynoate, monohydrochloride). SC-54684A (SC) is the pro-drug of the active compound, SC-54701A. Six healthy male subjects received 50 mg of SC (free base) and 2 received placebo (PBO). Results of the inhibition to ADP (20 μM) induced platelet aggregation are shown below:



Bleeding time increased a mean of 5.6 fold at 4 hrs post-dose and returned to within normal limits at 8 hrs after dosing. No significant changes in lab values or bleeding complications occurred. Peak serum concentrations coincided with peak PD effects of inhibition of platelet aggregation.

Conclusion; SC-54684A has a rapid onset of potent inhibition of platelet aggregation that is sustained for up to 10 hours after dosing.

931-114 Effects of Inhibition of Nitric Oxide Synthesis in Proximal and Distal Segments in Patients with Normal Arteries and in Patients with Coronary Artery Disease

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Inhibition of nitric oxide synthesis causes a decrease in basal diameter of distal epicardial coronary arteries in patients (pts) with normal coronary arteries (NCA). The effects of inhibition of nitric oxide synthesis with N^G-monomethyl-L-arginine (LNMMA) in atheromatous coronary arteries was evaluated in 13 pts with chronic stable angina (aged 57 ± 7 years, 11 males) due to angiographically documented coronary artery disease and in 8 pts (aged 50 ± 5 years, 4 males) with angiographically NCA. LNMMA was infused intracoronary at 4, 8 and 16 μmol/min each for 4 minutes. In response to low LNMMA, 4 μmol/min, there was a significant ($p < 0.05$) reduction in luminal diameter of both proximal (from 3.49 ± 0.28 to 3.35 ± 0.28 mm) and distal (from 1.33 ± 0.07 to 1.23 ± 0.06 mm) segments in patients with NCA. In patients with atheromatous arteries there was a reduction in diameter of the distal segments (from 1.44 ± 0.06 to 1.33 ± 0.07 mm) but no change occurred in the proximal segments (from 2.95 ± 0.16 to 2.89 ± 0.16 mm). In response to high LNMMA, 16 μmol/min, there was a significant ($p < 0.01$) reduction in luminal diameter of both proximal (from 2.53 ± 0.27 to 2.33 ± 0.26 mm) and distal (from 1.10 ± 0.06 to 0.99 ± 0.06 mm) segments in the pts with NCA. In the pts with atheromatous arteries the distal segments decreased in diameter (from 1.32 ± 0.07 to 1.17 ± 0.06 mm) but no change occurred in the proximal segments (from 3.16 ± 0.12 to 3.08 ± 0.14 mm). The magnitude of the distal vessel constriction was similar in both the patients with normal and in those with atheromatous arteries (−9.6 ± 2.1% and −10.9 ± 2.6% respectively, p = NS). In conclusion in pts with chronic stable angina due to coronary artery disease inhibition of basal nitric oxide synthesis causes distal coronary artery vasoconstriction, but it has no effect on proximal segments.

931-115 Phase I Studies on Inogatran, a New Selective Thrombin Inhibitor

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Inogatran is a new, synthetic, active site inhibitor of thrombin with a molecular weight of 439 dalton. Inogatran (pINN) selectively, rapidly and competitively binds thrombin with a Ki value of 15 nmol/l. *In vitro* it doubles the plasma